REMARKS

The Notice of Non-Compliant Amendment mailed December 12, 2005, has been received and reviewed. The Amendment of October 14, 2005, filed in response to the Final Office Action mailed June 15, 2005, was accompanied with an Request for Continued Examination pursuant to 37 C.F.R. 1.114, a copy of which is enclosed. Reconsideration is respectfully requested.

Claims 7, 10, 11, 19, 20-22, 24, 28-32 and 34 are amended, claims 23, 27, 33 and 35 are cancelled herein, and claim 36 is added herein. All cancellations and amendments are made without prejudice or disclaimer. Claims 1-6, 8, 9, 12-18 and 25 and 26 were previously cancelled. Applicants respectfully submit that no new matter has been added.

35 U.S.C. § 112, first paragraph, rejection maintained

Claims 20-24, 27-29 and 31-33 are rejected under 35 U.S.C. § 112, first paragraph. In the Office Action, the Examiner stated that the specification is enabling for a vaccine composition for protection against Salmonellosis compromising an immunologically effective amount of *Salmonella typhimurium* STMP mutated bacterium. However, the Office Action states that the specification does not reasonably enable "a vaccine composition for protection against Salmonellosis comprising an immunologically effective amount of any *Salmonella* mutated bacterium." (Final Office Action, page 2, No. 3).

More specifically, the Examiner alleges that the specification does not enable "1) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus-ovi, abortus-equi, derby, hadar, heidelberg, agona,* and *arizonae*, wherein said mutated bacterium lacking flagellin and wherein the vaccine is protective, 2) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus-ovi, abortus-equi, derby, hadar, heidelberg, agona,* and *arizonae*, wherein said mutated bacterium lacking flagellin and wherein the mutated bacterium is attenuated." *Id.*

Further, the Office Action repeats the citation of three references: Lockman et al., Wahden et al., and Hackett et al. At pages 4 to 6, the Office Action examines each of these references with the intent to show that the "role of attenuation to produce *Salmonella* nonflagelated mutants is unclear" and that the "skilled artisan is forced into undue

experimentation to practice (make and use) the invention as it is broadly claimed because the prior [art] has taught that many strains of fla$^-$ are not protective, do not confer protection from subsequent challenge by motile *Salmonella* bacteria and that mutations such as the flaF25 in the attenuation of Salmonella bacterium is unclear." (Office Action at page 6-7, underlining in original).

Claims 23, 27 and 33 have been cancelled herein thus making this rejection moot as to these claims. Applicants respectfully affirm that the specification is enabling for the full scope of the instant claims without undue experimentation.

A. The cited references fail to show that undue experimentation is necessary to practice the claimed invention.

Regarding the cited references, applicants assert that they fail to challenge the enablement of the claimed invention.

The Office Action characterizes Lockman as teaching "that flagella were necessary for *S. typhimurium* to invade and cause severe disease and the non-flagellated strains were equally proficient at colonization of the murine intestinal tract, but these mutants were deficient in invasion of the reticuloendothelial system." (Office Action, page 4). However, in the quoted statement Lockman is referring to "previous investigations" which Lockman is challenging. Lockman actually teaches that, while flagella and motility play a role in the ability of *S. typhimurium* to infect **tissue culture monolayers *in vitro***, flagella are not a virulence factor of *in vivo* murine typhoid. (Lockman *et al.*, page 142, 1st column). Moreover, Lockman found that the lethal dose (LD_{50}) of non-flagellated, non-motile *S. typhimurium* (*fli-8007::*Tn10) was nearly identical to that of the isogenic wild-type strains. *Id.* at 141, 2nd column. Accordingly, Lockman suggests that the presence or absence of flagella is irrelevant as a virulence factor for *Salmonella*. *Id.* at 142, 1st column.

Hackett is offered as allegedly showing a correlation between mice immunized with fla$^+$ *Salmonella* strains and protection from subsequent infection. (Office Action, page 8). However, Hackett teaches that multiple fla$^+$ strains do not confer protection—*S. typhimurium* M206 and *S. derby*. Additionally, in a discussion of Hackett, Lockman states that Hackett's non-flagellated mutant (*flaF25*) has a "mutation that not only involves some of the genes encoding the

biosynthesis of flagella, but extended into a previously undescribed virulence gene(s)." (*See,* Lockman at page 137, right column, lines 14-23). Similarly, Wahdan acknowledges "[i]t seems more probable that a property other than the synthesis of the flagellar antigen determines immunogenicity and is absent from this non-motile motif." (Wahdan, p. 72, right column, last lines). Moreover, it is uncertain that the 50 to 55 kDa protein discussed in Hackett is flagellin. As such, applicants respectfully assert, as was discussed in Lockman, Hackett, and Wahdan, that other factors are responsible for the lack of immunogenicity in Hackett, and not the absence of flagella.

Moreover, applicants also point out that that the fla^- strains in Hackett still conferred protection against motile *Salmonella*, and Hackett expressly discloses that both fla^+ and fla^- *Salmonella* strains induce cellular immunity—important in the defense against *Salmonella* infection. (Hackett, pages 82 and 83).

As such, the cited references actually support the fact that non-flagellated and/or non-motile *Salmonella* were known to maintain virulence and to illicit a protective immune response *in vivo*. There is nothing in the cited prior art suggesting that any of the *Salmonella* serotypes encompassed by the claimed invention would not be protective. Therefore, the cited references fail to show that one of skill in the art would have required undue experimentation to make and use the claimed invention.

Accordingly, applicants respectfully request removal of the rejection and reconsideration of the claims.

35 U.S.C. § 112, first paragraph, new grounds of rejection

Claims 7, 10-11, 19-24 and 27-35 stand rejected as allegedly containing subject matter not enabled by the specification. Claims 23, 27, 33 and 35 are cancelled herein making the rejection of these claims moot. Applicants respectfully traverse this rejection for the following reasons.

A. The specification is enabling for a vaccine comprising a mutated *Salmonella enterica.*

The specification would have allowed one of skill in the art to make and use the claimed

invention. The amended independent claims 7, 19, 22, 29 and 34 contain in part the element of a mutated *Salmonella enterica* bacterium. Those of skill in the art at the time of filing the instant application would have known that the genus *Salmonella* contains two species, each of which contains multiple serotypes. (Brenner FW, Villar RG, Angulo FJ, Tauxe R and B Swaminathan. *Salmonella* nomenclature. *Journal of Clinical Microbiology*, July 2000, p. 2465-2467). The two species are *S. enterica* and *S. bongori*. *S. enterica* is divided into six subspecies, the first being *S. enterica* subs. *enterica*. The subspecies contain serotypes usually named by the geographic location where they were first isolated, and grouped together because of their biochemical and genomic similarities. *Id.* at 2466. Many of the names for the serotypes are heterotypic synonyms, meaning that different names were given to the same bacterium. For example, it is generally accepted that *Salmonella enteritidis* and *Salmonella typhimurium* are heterotypic synonyms for *Salmonella enterica* subsp. *enterica*. Furthermore, the subspecies *S. enterica* subs. *enterica* includes the serotypes Typhimurium, Enteritidis, Choleraesuis, Dublin, Abortus-ovi, Abortus-equi, Derby, Hadar, Heidelberg and Agona. Accordingly, a reference to *S. enterica* is known by one of skill in the art, to include reference to the accompanying serotypes.

Moreover, for a claimed genus, such as *Salmonella enterica*, representative examples applicable to the genus as a whole are ordinarily enabling if one of skill in the art would expect the claimed genus could be used as disclosed in the specification without undue experimentation. (M.P.E.P. 2164.02). As such, the enablement of the claimed invention for a representative serotype of *S. enterica* subs. *enterica*, such as *S. typhimurium*, should be applicable and enabling to the other highly related or identical serotypes in the claimed invention.

Therefore, applicants submit that because the instant specification is enabled for a vaccine composition for protection against Salmonellosis comprising an immunologically effective amount of *Salmonella typhimurium* STMP mutated bacterium (Office Action, page 2), which is a serotype and heterotypic synonym of *Salmonella enterica* subsp. *enterica*, the specification is also enabling for one of skill in the art to make and use the claimed invention for the other serotypes of *Salmonella enterica* subsp. *enterica*.

B. Following the analysis in *In re Wands*, the specification is enabling for the claimed invention.

To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and use the scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Furthermore, simulated or prophetic examples are permitted in patent applications (M.P.E.P., § 608.01(p)(II)) and the use of prophetic examples may make a patent enabling. *Atlas Powder Co. v. E.I. DuPont di Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

When determining undue experimentation, the PTO and the courts look to the factors outlined in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The factors include 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

In *In re Wands*, the United States Court of Appeals, Federal Circuit (CAFC) reversed a rejection for lack of enablement for an application claiming monoclonal hybridomas which secrete specific antibodies. *Id.* at 740. The CAFC found the disclosure of the Wands patent enabling because there was a high level of skill in the monoclonal antibody art and, despite the relative unpredictable nature of the technology, the patent disclosure provided guidance and real working examples of the invention. *Id.* at 738.

The CAFC recognized the complexity of the inventive technology but disagreed with the PTO, reasoning that the existing working examples, along with the specification, would allow one of ordinary skill in the art to make and use the invention. *Id.* at 740. The CAFC stated that a considerable amount of experimentation is permissible if it is reasonable with regards to the nature of the art or if the specification provides a reasonable amount of guidance. *Id.* at 737. The CAFC reasoned that the specification contained considerable direction and guidance on how to practice the claimed invention, presented working examples, that all the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. *Id.*

Following the analysis from *In re Wands*, the specification of the instant invention also would have allowed one of skill in the art to make and use the claimed invention without undue experimentation. The specification discloses detailed laboratory protocols and guidance for the

full scope of the claims, the referenced methods are well known by those of skill in the art, there are numerous fla- *Salmonella enterica* mutants known in the art, working examples are disclosed using *Salmonella enterica* serotypes, and the level of skill in the art was high at the time of filing.

a. The specification includes working examples of non-flagellated mutant *Salmonella* marker vaccines in both chickens and pigs.

The specification is enabling for the claimed invention because it includes working examples of non-flagellated mutant *Salmonella* marker vaccines in both chickens and pigs.

Specifically, Example 3 of the specification demonstrates that chickens vaccinated with a non-motile mutant of *S. typhimurium* STMP, called *S. typhimurium* STM2000, were protected against a wild-type challenge infection. All the STM2000 vaccinated chickens survived compared to an 80% death rate for those inoculated with a wild-type *S. typhimurium*. Thus demonstrating the successful immunogenicity of flagella-less *S. typhimurium* in chickens.

Example 4, at pages 22-23 of the specification, shows that the live attenuated flagella-less *S. typhimurium* STM2000 vaccine significantly reduced fecal shedding in pigs after a challenge infection with a wild-type *S. typhimurium* serotype. Thus demonstrating the successful immunogenicity of flagella-less *S. typhimurium* in pigs.

Another working example is provided by Example 2, at page 18 of the specification, which discloses vaccines comprising flagellated and non-flagellated *S. enteritidis* , specifically *S. enteritidis* fla^+ and *S. enteritidis* fla^-. The results of Example 2 show that chickens vaccinated with the *S. enteritidis* fla^- vaccines were negative for antibodies to the flagellin protein of *S. enteritidis* thus giving a clearly recognizable marker over those chickens vaccinated with the *S. enteritidis* fla^+ vaccine.

The specification also provides detailed instructions for selecting non-motile mutant from serotype *S. typhimurium* SL3261. (Example 1, page 17). In this example, a flagellin protein gene of *S. typhimurium* SL3261 was chemically mutagenized with NTG and non-motile mutants were selected by light microscopy. The selected mutant was named STM2001 and subsequent electrophoretic analysis revealed that the mutant lacked the flagellin protein fragment of 51kDa and pI 4.7, as compared to the non-mutant parent serotype. *Id.*

Furthermore, applicants respectfully submit that it is not necessary to point out specific nucleotide mutations in the flagellin gene or biosynthesis pathway. Independent claims 7, 19, 22, 29 and 34 contain, in part, the element "wherein said live mutated bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin in the subject to which it is administered." The scope of the claims does not extend to a specific mutation but to a mutated phenotype wherein the mutated bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin. The specification is clearly enabling for the process of mutating a *S. enterica* bacterium and for selecting the mutated phenotype. As such, it is not necessary to show which nucleotides are deleted, substituted or inserted.

Therefore, the instant specification provides multiple working examples of flagella-less and non-motile mutate *S. enterica* serotypes and would have allowed one of ordinary skill in the art to make and use effective marker vaccines.

b. All the methods disclosed in the specification are well known in the art and the level of skill in the art was high at the time of filing the application.

All the methods needed to practice the claimed invention are well known and there was a high level of skill in the art at the time the application was filed.

One of the disclosed methods is chemical mutagenesis, a technique well known in the art. (Specification, page 7, citing Andersen, P. 1995. *Mutagenesis*, p 31-58 in Methods in Cell Biology). For chemical mutagenesis of the flagellin gene or other known genes involved in the flagellum-biosynthesis pathway used by *S. enterica* serotypes, the bacterium are grown on blood agar selective medium and to the culture is added trioxalen (a commercially available chemical mutagen) and then the suspension is irradiated with U.V. 365 nm light. (Specification, page 15, example 1). Next, non-motile/flagella-less (fla-) mutants are easily selected with a light microscope by looking for a lack of motility and/or the absence of flagella. (Specification, page 7).

Using the chemical mutagenesis method, applicants isolated a non-motile mutant of *S. typhimurium* STMP named STM2000. *Id.* In a different experiment following the same method, *S. typhimurium* SL3261 was chemically mutagenized with NTG. *Id.* at 17. The mutant STM2001 was isolated and found to have a specific flagellin mutation shown by the lack of the flagellin spot of 51kDa and pI 4.7, as compared to its parent strain. *Id.*

Alternatively, the specification outlines another standard method known in the art for fla- selection using monoclonal antibodies to select for bacteria lacking at least one antigenic determinant of flagellin. *Id.*

A second disclosed method allows for the introduction of a mutation at a predetermined nucleic acid site in a flagellin gene and/or a flagellum-biosynthesis gene. (Specification, page 8). This method relies on well-known recombinant DNA techniques by which the natural gene sequence may be disrupted or foreign DNA may be artificially introduced by homologous recombination such that the mutant cell survives but it is abnormal for the mutant gene product. (*See*, Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. D. Recombinant DNA Technology. In Molecular Biology of the Cell (B. Alberts, ed.), pp. 325-326. New York, Garland Publishing, Inc., 1994). The recombinant DNA techniques used in the construction of fla$^-$ mutants are well-known standard techniques involving the cloning of the flagellin gene, modification of the gene sequence by site-directed mutagenesis, restriction enzyme digestion followed by relegation or PCR-approaches. (Specification, page 8 citing Sambrook, J. *et al.* Molecular Cloning: a laboratory manual. ISBN 0-8769-309-6). Furthermore, these recombinant DNA techniques may be performed using commercial recombination kits such as the Transformer® kit sold by Clonetech. (Specification, page 9).

The level of skill in the art is high, evidenced by the many genes and gene clusters involved in the flagellum-biosynthesis pathway that were described in the art. (Specification, page 6). In addition, the flagellin genes had been described for *S. enterica, S. enteritidis, S. dublin, S. typhimurium,* and *S. abortus-equi. Id.* Additionally, the flagellin genes of novel *Salmonella* species can easily be found using standard hybridization techniques based on homology with known *Salmonella* flagellin genes. *Id.*

The level of skill in the art at the time of filing is also evidenced by the disclosure of the reference Kutsukake *et al.* In Kutsukake, Mu d1(Ap^r Lac) *c*ts62 and Tn*10* insertion mutants for

nearly all the flagellar genes in serotypes of *S. typhimurium* are disclosed. (Kutsukake *et al.*, pages 741-742). Kutsukake also discloses partial DNA sequence from flagellar operons of *S. typhimurium*. *Id.* at 745. As such, Kutsukake shows that there was detailed knowledge about the genes involved in the flagellar biosynthesis pathway allowing one of skill in the art to make and use the claimed invention without undue experimentation.

And lastly, despite the existence of numerous flagellar genes, there are only two flagellin protein genes in wild-type flagellum-bearing *Salmonella enterica* serotypes. *Id.* Of these two well known genes, only one is active and producing flagellin at a time. *Id.* As such, those of skill in the art could have easily constructed flagellin mutants by a routine mutagenesis of the two well known flagellin genes.

Therefore, the specification is enabling for the scope of the instant claims because, like in *In re Wands*, the recombinant DNA techniques are predictable and well known in the art, the specification provides significant and detailed guidance and includes real working examples applicable to the entire scope of the claimed invention.

For the reasons presented herein, applicants respectfully request removal of the rejection of claims 20-24, 27-29 and 31-33 and ask reconsideration of the claims.

CONCLUSION

In view of the foregoing, applicants respectfully request removal of the rejections and kindly ask reconsideration of the claims. Claims 7, 10, 11, 19-22, 24, 28-32, 34 and 36 are believed to be in condition for allowance and an early notice thereof is kindly requested. If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' agent at the address or telephone number given herein.

Respectfully submitted,

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Attorney for Applicants
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Date: December 14, 2005
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OIPE IAP28 OCT 15 2005 PATENT & TRADEMARK OFFICE

Invention:	SALMONELLA VACCINE
Applicant(s):	Nuijten et al.
Filing Date:	December 27, 2000
Serial No.:	09/749,025
Date Sent:	October 14, 2005 via Express Mail Label No. EL994842727US
Docket No.: YMC/alb	2990-5048US

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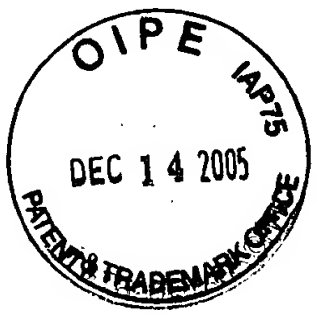

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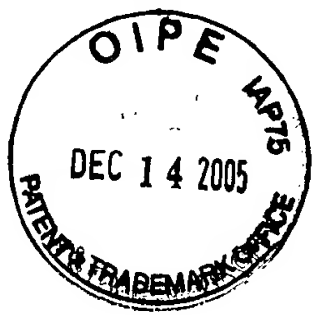

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional)
2990-5048US

In re Application of Nuijten et al.	
Application Number 09/749,025	Filed December 27, 2000
For SALMONELLA VACCINE	
Group Art Unit 1645	Examiner V. Ford

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a response in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☒	One month (37 CFR 1.17(a)(1))	$120.00
☐	Two months (37 CFR 1.17(a)(2))	$_____
☐	Three months (37 CFR 1.17(a)(3))	$_____
☐	Four months (37 CFR 1.17(a)(4))	$_____
☐	Five months (37 CFR 1.17(a)(5))	$_____

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ _____.

☒ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1469.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a).

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October 14, 2005
Date

Signature

Yury M. Colton, Ph.D. Reg. No. 55,081
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

CERTIFICATE OF MAILING

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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

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Application Number	09/749,025
Filing Date	December 27, 2000
First Named Inventor	Nuijten et al.
Art Unit	1645
Examiner Name	V. Ford
Attorney Docket Number	2990-5048US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114

a. ☐ Previously submitted
   i. ☐ Consider the amendment(s)/reply under 37 C.F.R. 1.116 previously filed on _____
   (Any unentered amendment(s) referred to above will be entered).
   ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   iii. ☐ Other _____

b. Enclosed
   i. ☒ Amendment/Reply
   ii ☐ Affidavit(s)/Declaration(s)
   iii. ☐ Information Disclosure Statement (IDS)
   iv. ☐ Other _____

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge any deficiency in the following fees, or credit any overpayments, to Deposit Account No. 20-1469
   i. ☒ RCE fee required under 37 C.F.R. 1.17(e)
   ii. ☐ Extension of time fee (37 C.F.R. 1.136 and 1.17)
   iii. ☐ Other _____

b. ☒ Check in the amount of $790.00 enclosed

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Name (Print /Type)	Yury M. Colton, Ph.D.	*Registration No. (Attorney/Agent)*	55,081
Signature		*Date*	October 14, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Nuijten et al.

Serial No.: 09/749,025

Filed: December 27, 2000

For: SALMONELLA VACCINE

Confirmation No.: 6121

Examiner: V. Ford

Group Art Unit: 1645

Attorney Docket No.: 2990-5048US

NOTICE OF EXPRESS MAILING

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AMENDMENT and REQUEST FOR CONTINUED EXAMINATION PURSUANT TO 37 C.F.R. 1.114

Box RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Final Office Action mailed June 16, 2005, applicants submit the following amendments and remarks.

Amendments to the Claims are reflected in the listing which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

IN THE CLAIMS:

All claims currently pending and under construction in the referenced application are shown below. Please enter these claims as amended. This listing of claims will replace all prior versions and listings of claims in the application.

Claims 7, 11, 10, 19, 20-22, 24, 28-32 and 34 are amended, claims 23, 27, 33 and 35 are canceled, and claim 36 is added herein. All cancellations and amendments are made without prejudice or disclaimer. Claims 1 to 6, 12 to 18 and 25 and 26 were previously canceled. Applicants respectfully submit that no new matter has been added.

Listing of Claims:

Claims 1 to 6 (Canceled).

7. (Currently amended) An immunogenic composition for marking an exposure of a subject to wild-type *Salmonella*, said immunogenic composition comprising:

an immunologically effective amount of a live mutated bacterium[[;]] and a pharmaceutically acceptable carrier; ~~and an adjuvant,~~;

wherein, said live mutated bacterium ~~being~~ is ~~selected from the group consisting of the~~ *Salmonella enterica* ~~species *typhimurium, enteritidis, choleraesuis, dublin, abortus ovi, abortus equi, derby, hadar, heidelberg, agona,* and *arizonae,*~~ that in its wild-type form carries flagella[[,]];and

wherein said live mutated bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin in the subject to which it is administered. ~~due to a mutation in a gene of the flagellar biogenesis pathway, said bacterium being in live attenuated form.~~

10. (Currently amended) The immunogenic composition according to claim 7, further comprising:

~~wherein the~~ an adjuvant ~~is~~ selected from the group consisting of Freunds Complete adjuvant, Freunds Incomplete adjuvant, vitamin E, non-ionic block polymers,

muramyldipeptides, immune stimulating complexes, saponins, mineral oil, vegetable oil, Carbopol, *E. coli* heat-labile toxin, *Cholera* toxin, aluminum hydroxide, aluminum phosphate, aluminum oxide, oil-emulsions, and vitamin-E solubilisate.

11. (Currently amended) The immunogenic composition according to claim 7, wherein the immunogenic composition is in a freeze-dried or spray-dried form.

19. (Currently amended) An immunogenic composition for marking an exposure of a subject to wild-type *Salmonella*, said immunogenic composition comprising:

an immunologically effective amount of ~~a~~ an inactivated mutated bacterium, a pharmaceutically acceptable carrier, ~~and an adjuvant,~~;

wherein said inactivated mutated bacterium ~~being~~ is ~~selected from the group consisting of~~ ~~the~~ *Salmonella enterica* ~~species *typhimurium, enteritidis, choleraesuis, dublin, abortus ovi, abortus equi, derby, hadar, heidelberg, agona,* and *arizonae*~~, that in its wild-type form carries flagella[[,]] ; and

wherein said inactivated mutated bacterium ~~lacking at least one antigenic determinant of flagellin and not being capable of inducing an immune response to flagellin due to a mutation in a gene of the flagellar biogenesis pathway,~~ is not capable of inducing an immune response to at least one antigenic determinant of flagellin in the subject to which it is administered ~~and said mutated bacterium being inactivated~~.

20. (Currently amended) A ~~vaccine for the protection of animals against Salmonellosis strains,~~ composition comprising:

an immunologically effective amount of a live mutated *Salmonella typhimurium* ~~bacterium~~, wherein the wild-type form of the live mutated *S. typhimurium* ~~that in its wild type form~~ carries flagella[[,]];

wherein said live mutated ~~*Salmonella*~~ *S. typhimurium* ~~bacterium~~ is not capable of inducing an immune response to at least one antigenic determinant of flagellin in a subject to which it is administered ~~due to a mutation in a gene of the flagellar biogenesis pathway and being in live attenuated form, and~~ ; and

a pharmaceutically acceptable carrier comprising water, a solution of physiological salt concentration, SPGA, sorbitol, mannitol, starch, sucrose, glucose, dextran, albumin, casein, bovine serum, skim milk, or phosphate buffer.

21. (Currently amended) A ~~vaccine for the protection of animals against Salmonellosis strains,~~ composition comprising:

an immunologically effective amount of a mutated *Salmonella typhimurium* ~~bacterium,~~ wherein the wild type form of the mutated *S. typhimurium* ~~that in its wild type form~~ carries flagella[[,]];

wherein said mutated ~~*Salmonella*~~ *S. typhimurium* ~~bacterium~~ is lacking flagellin and ~~comprising~~ comprises an immunologically effective amount of a ~~*Salmonella*~~ *S. typhimurium* strain STMP mutated bacterium[[,]] ; and

a pharmaceutically acceptable carrier.

22. (Currently amended) An improved *Salmonella* vaccine, having an immunologically effective amount of a *Salmonella enterica* bacterium ~~and~~ in a pharmaceutically acceptable carrier, the improvement comprising:

the *Salmonella enterica* bacterium comprising an inactivated mutated bacterium that in its wild type form carries flagella, but in its mutated form is no longer capable ~~to induce~~ of inducing an immune response to at least one antigenic determinant of flagellin in a subject to which it is administered ~~an animal, said mutated bacterium including a mutation in a gene of the bacterium's flagellar biogenesis pathway; and an adjuvant~~.

23. (Cancelled)

24. (Currently amended) The improved *Salmonella* vaccine of claim 22, wherein the inactivated mutated bacterium lacks flagellin.

27. (Cancelled)

28. (Currently amended) The improved *Salmonella* vaccine of claim 22, wherein the improved *Salmonella* vaccine is in a freeze-dried or spray-dried form.

29. (Currently amended) An improvement in a marker vaccine, comprising a *Salmonella enterica* bacterium, the improvement comprising:

an immunologically effective amount of a mutated *Salmonella enterica*, wherein the wild type form of the mutated *Salmonella enterica* ~~bacterium that in its wild type form~~ carries flagella[[,]];

wherein said mutated *Salmonella enterica* bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin in a subject to which it is administered ~~due to a mutation in a gene of the flagellar biogenesis pathway and being selected from the group consisting of the *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus ovi, abortus equi, derby, hadar, heidelberg, agona,* and *arizonae*, and~~;

a pharmaceutically acceptable carrier[[,]] ; and

wherein the marker vaccine is in a freeze-dried or spray-dried form.

30. (Currently amended) The immunogenic composition according to claim 19, wherein the immunogenic composition is in a freeze-dried or spray-dried form.

31. (Currently amended) The improved marker vaccine of claim 29, wherein the mutated *Salmonella enterica* ~~bacterium~~ is in live attenuated form.

32. (Currently amended) The improved marker vaccine of claim 29, wherein the mutated *Salmonella enterica* ~~bacterium~~ lacks flagellin.

33. (Cancelled)

34. (Currently amended) In an immunogenic composition including a *Salmonella* bacterium, the improvement comprising:

a lyophilized immunogenic composition comprising a mutated *Salmonella enterica;*

~~bacterium, said *Salmonella* bacterium selected from the group consisting of the *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus ovi, abortus equi, derby, hadar, heidelberg, agona,* and *arizonae,*~~

said *Salmonella* *enterica* ~~bacterium~~ in its wild type form carrying flagella[[,]]; and

said mutated *Salmonella* *enterica* ~~bacterium~~ lacking at least one antigenic determinant of flagellin and not being capable of inducing an immune response to the at least one antigenic determinant of flagellin in a subject to which it is administered ~~due to a mutation in a gene of the flagellar biogenesis pathway~~.

35. (Cancelled)

36. (New) A composition comprising:

an immunologically effective amount of a mutated *S. typhimurium*, wherein the wild type form of the mutated *S. typhimurium* carries flagella;

wherein said mutated *S. typhimurium* comprises an immunologically effective amount of a *S. typhimurium* strain STMP mutated bacterium; and

a pharmaceutically acceptable carrier.

REMARKS

The Final Office Action mailed June 15, 2005, has been received and reviewed. Accompanying this response is a Request for Continued Examination pursuant to 37 C.F.R. 1.114. Reconsideration is respectfully requested.

Claims 7, 10, 11, 19, 20-22, 24, 28-32 and 34 are amended, claims 23, 27, 33 and 35 are canceled, and claim 36 is added herein. All cancellations and amendments are made without prejudice or disclaimer. Claims 1 to 6, 12 to 18 and 25 and 26 were previously canceled. Applicants respectfully submit that no new matter has been added.

35 U.S.C. § 112, first paragraph, rejection maintained

Claims 20-24, 27-29 and 31-33 are rejected under 35 U.S.C. § 112, first paragraph. In the Office Action, the Examiner stated that the specification is enabling for a vaccine composition for protection against Salmonellosis compromising an immunologically effective amount of *Salmonella typhimurium* STMP mutated bacterium. However, the Office Action states that the specification does not reasonably enable "a vaccine composition for protection against Salmonellosis comprising an immunologically effective amount of any *Salmonella* mutated bacterium." (Final Office Action, page 2, No. 3).

More specifically, the Examiner alleges that the specification does not enable "1) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus-ovi, abortus-equi, derby, hadar, heidelberg, agona,* and *arizonae*, wherein said mutated bacterium lacking flagellin and wherein the vaccine is protective, 2) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus-ovi, abortus-equi, derby, hadar, heidelberg, agona,* and *arizonae*, wherein said mutated bacterium lacking flagellin and wherein the mutated bacterium is attenuated." *Id.*

Further, the Office Action repeats the citation of three references: Lockman et al., Wahden et al., and Hackett et al. At pages 4 to 6, the Office Action examines each of these references with the intent to show that the "role of attenuation to produce *Salmonella* nonflagelated mutants is unclear" and that the "skilled artisan is forced into undue experimentation to practice (make and use) the invention as it is broadly claimed because the

prior [art] has taught that many strains of fla$^-$ are not protective, do not confer protection from subsequent challenge by motile *Salmonella* bacteria and that mutations such as the flaF25 in the attenuation of Salmonella bacterium is unclear." (Office Action at page 6-7, underlining in original).

Claims 23, 27 and 33 have been cancelled herein thus making this rejection moot as to these claims. Applicants respectfully affirm that the specification is enabling for the full scope of the instant claims without undue experimentation.

A. The cited references fail to show that undue experimentation is necessary to practice the claimed invention.

Regarding the cited references, applicants assert that they fail to challenge the enablement of the claimed invention.

The Office Action characterizes Lockman as teaching "that flagella were necessary for *S. typhimurium* to invade and cause severe disease and the non-flagellated strains were equally proficient at colonization of the murine intestinal tract, but these mutants were deficient in invasion of the reticuloendothelial system." (Office Action, page 4). However, in the quoted statement Lockman is referring to "previous investigations" which Lockman is challenging. Lockman actually teaches that, while flagella and motility play a role in the ability of *S. typhimurium* to infect **tissue culture monolayers *in vitro***, flagella are not a virulence factor of *in vivo* murine typhoid. (Lockman *et al.*, page 142, 1st column). Moreover, Lockman found that the lethal dose (LD_{50}) of non-flagellated, non-motile *S. typhimurium* (*fli-8007::*Tn10) was nearly identical to that of the isogenic wild-type strains. *Id.* at 141, 2nd column. Accordingly, Lockman suggests that the presence or absence of flagella is irrelevant as a virulence factor for *Salmonella*. *Id.* at 142, 1st column.

Hackett is offered as allegedly showing a correlation between mice immunized with fla$^+$ *Salmonella* strains and protection from subsequent infection. (Office Action, page 8). However, Hackett teaches that multiple fla$^+$ strains do not confer protection—*S. typhimurium* M206 and *S. derby*. Additionally, in a discussion of Hackett, Lockman states that Hackett's non-flagellated mutant (*flaF25*) has a "mutation that not only involves some of the genes encoding the biosynthesis of flagella, but extended into a previously undescribed virulence gene(s)." (*See,*

Lockman at page 137, right column, lines 14-23). Similarly, Wahdan acknowledges "[i]t seems more probable that a property other than the synthesis of the flagellar antigen determines immunogenicity and is absent from this non-motile motif." (Wahdan, p. 72, right column, last lines). Moreover, it is uncertain that the 50 to 55 kDa protein discussed in Hackett is flagellin. As such, applicants respectfully assert, as was discussed in Lockman, Hackett, and Wahdan, that other factors are responsible for the lack of immunogenicity in Hackett, and not the absence of flagella.

Moreover, applicants also point out that that the fla^- strains in Hackett still conferred protection against motile *Salmonella*, and Hackett expressly discloses that both fla^+ and fla^- *Salmonella* strains induce cellular immunity—important in the defense against *Salmonella* infection. (Hackett, pages 82 and 83).

As such, the cited references actually support the fact that non-flagellated and/or non-motile *Salmonella* were known to maintain virulence and to illicit a protective immune response *in vivo*. There is nothing in the cited prior art suggesting that any of the *Salmonella* serotypes encompassed by the claimed invention would not be protective. Therefore, the cited references fail to show that one of skill in the art would have required undue experimentation to make and use the claimed invention.

Accordingly, applicants respectfully request removal of the rejection and reconsideration of the claims.

35 U.S.C. § 112, first paragraph, new grounds of rejection

Claims 7, 10-11, 19-24 and 27-35 stand rejected as allegedly containing subject matter not enabled by the specification. Claims 23, 27, 33 and 35 are cancelled herein making the rejection of these claims moot. Applicants respectfully traverse this rejection for the following reasons.

A. The specification is enabling for a vaccine comprising a mutated *Salmonella enterica.*

The specification would have allowed one of skill in the art to make and use the claimed invention. The amended independent claims 7, 19, 22, 29 and 34 contain in part the element of a

mutated *Salmonella enterica* bacterium. Those of skill in the art at the time of filing the instant application would have known that the genus *Salmonella* contains two species, each of which contains multiple serotypes. (Brenner FW, Villar RG, Angulo FJ, Tauxe R and B Swaminathan. *Salmonella* nomenclature. *Journal of Clinical Microbiology*, July 2000, p. 2465-2467). The two species are *S. enterica* and *S. bongori*. *S. enterica* is divided into six subspecies, the first being *S. enterica* subs. *enterica*. The subspecies contain serotypes usually named by the geographic location where they were first isolated, and grouped together because of their biochemical and genomic similarities. *Id.* at 2466. Many of the names for the serotypes are heterotypic synonyms, meaning that different names were given to the same bacterium. For example, it is generally accepted that *Salmonella enteritidis* and *Salmonella typhimurium* are heterotypic synonyms for *Salmonella enterica* subsp. *enterica.* Furthermore, the subspecies *S. enterica* subs. *enterica* includes the serotypes Typhimurium, Enteritidis, Choleraesuis, Dublin, Abortus-ovi, Abortus-equi, Derby, Hadar, Heidelberg and Agona. Accordingly, a reference to *S. enterica* is known by one of skill in the art, to include reference to the accompanying serotypes.

Moreover, for a claimed genus, such as *Salmonella enterica*, representative examples applicable to the genus as a whole are ordinarily enabling if one of skill in the art would expect the claimed genus could be used as disclosed in the specification without undue experimentation. (M.P.E.P. 2164.02). As such, the enablement of the claimed invention for a representative serotype of *S. enterica* subs. *enterica*, such as *S. typhimurium*, should be applicable and enabling to the other highly related or identical serotypes in the claimed invention.

Therefore, applicants submit that because the instant specification is enabled for a vaccine composition for protection against Salmonellosis comprising an immunologically effective amount of *Salmonella typhimurium* STMP mutated bacterium (Office Action, page 2), which is a serotype and heterotypic synonym of *Salmonella enterica* subsp. *enterica*, the specification is also enabling for one of skill in the art to make and use the claimed invention for the other serotypes of *Salmonella enterica* subsp. *enterica*.

B. Following the analysis in *In re Wands*, the specification is enabling for the claimed invention.

To satisfy the enablement requirement, a specification must teach those skilled in the art

how to make and use the scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Furthermore, simulated or prophetic examples are permitted in patent applications (M.P.E.P., § 608.01(p)(II)) and the use of prophetic examples may make a patent enabling. *Atlas Powder Co. v. E.I. DuPont di Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

When determining undue experimentation, the PTO and the courts look to the factors outlined in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The factors include 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

In *In re Wands*, the United States Court of Appeals, Federal Circuit (CAFC) reversed a rejection for lack of enablement for an application claiming monoclonal hybridomas which secrete specific antibodies. *Id.* at 740. The CAFC found the disclosure of the Wands patent enabling because there was a high level of skill in the monoclonal antibody art and, despite the relative unpredictable nature of the technology, the patent disclosure provided guidance and real working examples of the invention. *Id.* at 738.

The CAFC recognized the complexity of the inventive technology but disagreed with the PTO, reasoning that the existing working examples, along with the specification, would allow one of ordinary skill in the art to make and use the invention. *Id.* at 740. The CAFC stated that a considerable amount of experimentation is permissible if it is reasonable with regards to the nature of the art or if the specification provides a reasonable amount of guidance. *Id.* at 737. The CAFC reasoned that the specification contained considerable direction and guidance on how to practice the claimed invention, presented working examples, that all the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. *Id.*

Following the analysis from *In re Wands*, the specification of the instant invention also would have allowed one of skill in the art to make and use the claimed invention without undue experimentation. The specification discloses detailed laboratory protocols and guidance for the full scope of the claims, the referenced methods are well known by those of skill in the art, there

are numerous fla- *Salmonella enterica* mutants known in the art, working examples are disclosed using *Salmonella enterica* serotypes, and the level of skill in the art was high at the time of filing.

a. The specification includes working examples of non-flagellated mutant *Salmonella* marker vaccines in both chickens and pigs.

The specification is enabling for the claimed invention because it includes working examples of non-flagellated mutant *Salmonella* marker vaccines in both chickens and pigs.

Specifically, Example 3 of the specification demonstrates that chickens vaccinated with a non-motile mutant of *S. typhimurium* STMP, called *S. typhimurium* STM2000, were protected against a wild-type challenge infection. All the STM2000 vaccinated chickens survived compared to an 80% death rate for those inoculated with a wild-type *S. typhimurium*. Thus demonstrating the successful immunogenicity of flagella-less *S. typhimurium* in chickens.

Example 4, at pages 22-23 of the specification, shows that the live attenuated flagella-less *S. typhimurium* STM2000 vaccine significantly reduced fecal shedding in pigs after a challenge infection with a wild-type *S. typhimurium* serotype. Thus demonstrating the successful immunogenicity of flagella-less *S. typhimurium* in pigs.

Another working example is provided by Example 2, at page 18 of the specification, which discloses vaccines comprising flagellated and non-flagellated *S. enteritidis* , specifically *S. enteritidis* fla^+ and *S. enteritidis* fla^-. The results of Example 2 show that chickens vaccinated with the *S. enteritidis* fla^- vaccines were negative for antibodies to the flagellin protein of *S. enteritidis* thus giving a clearly recognizable marker over those chickens vaccinated with the *S. enteritidis* fla^+ vaccine.

The specification also provides detailed instructions for selecting non-motile mutant from serotype *S. typhimurium* SL3261. (Example 1, page 17). In this example, a flagellin protein gene of *S. typhimurium* SL3261 was chemically mutagenized with NTG and non-motile mutants were selected by light microscopy. The selected mutant was named STM2001 and subsequent electrophoretic analysis revealed that the mutant lacked the flagellin protein fragment of 51kDa and pI 4.7, as compared to the non-mutant parent serotype. *Id.*

Furthermore, applicants respectfully submit that it is not necessary to point out specific nucleotide mutations in the flagellin gene or biosynthesis pathway. Independent claims 7, 19, 22, 29 and 34 contain, in part, the element "wherein said live mutated bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin in the subject to which it is administered." The scope of the claims does not extend to a specific mutation but to a mutated phenotype wherein the mutated bacterium is not capable of inducing an immune response to at least one antigenic determinant of flagellin. The specification is clearly enabling for the process of mutating a *S. enterica* bacterium and for selecting the mutated phenotype. As such, it is not necessary to show which nucleotides are deleted, substituted or inserted.

Therefore, the instant specification provides multiple working examples of flagella-less and non-motile mutate *S. enterica* serotypes and would have allowed one of ordinary skill in the art to make and use effective marker vaccines.

b. All the methods disclosed in the specification are well known in the art and the level of skill in the art was high at the time of filing the application.

All the methods needed to practice the claimed invention are well known and there was a high level of skill in the art at the time the application was filed.

One of the disclosed methods is chemical mutagenesis, a technique well known in the art. (Specification, page 7, citing Andersen, P. 1995. *Mutagenesis*, p 31-58 in Methods in Cell Biology). For chemical mutagenesis of the flagellin gene or other known genes involved in the flagellum-biosynthesis pathway used by *S. enterica* serotypes, the bacterium are grown on blood agar selective medium and to the culture is added trioxalen (a commercially available chemical mutagen) and then the suspension is irradiated with U.V. 365 nm light. (Specification, page 15, example 1). Next, non-motile/flagella-less (fla-) mutants are easily selected with a light microscope by looking for a lack of motility and/or the absence of flagella. (Specification, page 7).

Using the chemical mutagenesis method, applicants isolated a non-motile mutant of *S. typhimurium* STMP named STM2000. *Id.* In a different experiment following the same method, *S. typhimurium* SL3261 was chemically mutagenized with NTG. *Id.* at 17. The mutant STM2001 was isolated and found to have a specific flagellin mutation shown by the lack of the flagellin spot of 51kDa and pI 4.7, as compared to its parent strain. *Id.*

Alternatively, the specification outlines another standard method known in the art for fla- selection using monoclonal antibodies to select for bacteria lacking at least one antigenic determinant of flagellin. *Id.*

A second disclosed method allows for the introduction of a mutation at a predetermined nucleic acid site in a flagellin gene and/or a flagellum-biosynthesis gene. (Specification, page 8). This method relies on well-known recombinant DNA techniques by which the natural gene sequence may be disrupted or foreign DNA may be artificially introduced by homologous recombination such that the mutant cell survives but it is abnormal for the mutant gene product. (*See*, Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. D. Recombinant DNA Technology. In Molecular Biology of the Cell (B. Alberts, ed.), pp. 325-326. New York, Garland Publishing, Inc., 1994). The recombinant DNA techniques used in the construction of fla⁻ mutants are well-known standard techniques involving the cloning of the flagellin gene, modification of the gene sequence by site-directed mutagenesis, restriction enzyme digestion followed by relegation or PCR-approaches. (Specification, page 8 citing Sambrook, J. *et al.* Molecular Cloning: a laboratory manual. ISBN 0-8769-309-6). Furthermore, these recombinant DNA techniques may be performed using commercial recombination kits such as the Transformer® kit sold by Clonetech. (Specification, page 9).

The level of skill in the art is high, evidenced by the many genes and gene clusters involved in the flagellum-biosynthesis pathway that were described in the art. (Specification, page 6). In addition, the flagellin genes had been described for *S. enterica, S. enteritidis, S. dublin, S. typhimurium,* and *S. abortus-equi. Id.* Additionally, the flagellin genes of novel *Salmonella* species can easily be found using standard hybridization techniques based on homology with known *Salmonella* flagellin genes. *Id.*

The level of skill in the art at the time of filing is also evidenced by the disclosure of the reference Kutsukake *et al.* In Kutsukake, Mu d1(Ap^r Lac) *c*ts62 and Tn*10* insertion mutants for

nearly all the flagellar genes in serotypes of *S. typhimurium* are disclosed. (Kutsukake *et al.*, pages 741-742). Kutsukake also discloses partial DNA sequence from flagellar operons of *S. typhimurium*. *Id.* at 745. As such, Kutsukake shows that there was detailed knowledge about the genes involved in the flagellar biosynthesis pathway allowing one of skill in the art to make and use the claimed invention without undue experimentation.

And lastly, despite the existence of numerous flagellar genes, there are only two flagellin protein genes in wild-type flagellum-bearing *Salmonella enterica* serotypes. *Id.* Of these two well known genes, only one is active and producing flagellin at a time. *Id.* As such, those of skill in the art could have easily constructed flagellin mutants by a routine mutagenesis of the two well known flagellin genes.

Therefore, the specification is enabling for the scope of the instant claims because, like in *In re Wands*, the recombinant DNA techniques are predictable and well known in the art, the specification provides significant and detailed guidance and includes real working examples applicable to the entire scope of the claimed invention.

For the reasons presented herein, applicants respectfully request removal of the rejection of claims 20-24, 27-29 and 31-33 and ask reconsideration of the claims.

CONCLUSION

In view of the foregoing, applicants respectfully request removal of the rejections and kindly ask reconsideration of the claims. Claims 7, 10, 11, 19-22, 24, 28-32, 34 and 36 are believed to be in condition for allowance and an early notice thereof is kindly requested. If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' agent at the address or telephone number given herein.

Respectfully submitted,

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YMC/ymc